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(54) Title: NOVEL USES OF MEVALONATE PATHWAY BLOCKERS

(57) Abstract: Statins are able to block the mevalonate pathway at an early stage, preventing build up of isopentenyl pyrophosphate by nitrogen containing bisphosphonates by blocking the pathway further downstream, with medicaments containing statins being administered at an appropriate time being able to thereby prevent the build up of IPP, which has been found to activate $\gamma\delta$ T cells and cause the acute phase response associated with the nitrogen containing bisphosphonates.

INTERNATIONAL SEARCH REPORT

Inte
al Application No
PC, 002004/005019

A. CLASSIFICATION OF SUBJECT MATTER

| | | | | | |
|----------|------------|------------|-----------|------------|------------|
| IPC 7 | A61K31/366 | A61K31/336 | A61K31/40 | A61K31/405 | A61K31/663 |
| A61P3/10 | A61P19/00 | A61K45/06 | | | |

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| X | <p>EP 1 127 573 A (PFIZER PRODUCTS INC) 29 August 2001 (2001-08-29) cited in the application paragraphs '0016!, '0017!; claims 1-5, 9, 10 paragraph '0021! paragraphs '0023! - '0036! paragraphs '0046! - '0048! paragraph '0059!</p> | 1-6,8-19 |
| X | <p>WO 99/45923 A (MERCK & CO., INC; FISHER, JOHN, E; RODAN, GIDEON, A) 16 September 1999 (1999-09-16) cited in the application page 1, lines 17-22; claims 1-13, 16-19, 23-25 pages 4-5; examples 2-6</p> | 1-6,8-19 |
| | | -/- |

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

• Special categories of cited documents :

- A* document defining the general state of the art which is not considered to be of particular relevance
- E* earlier document but published on or after the international filing date
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- X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- Z* document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/GB2004/005019

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|--|--|----------------------------------|
| Category | Category | Relevant to claim No. |
| X | STEWART G ET AL: "Delayed gastrointestinal complications associated with alendronate: A case involving an elderly nursing home resident" CANADIAN JOURNAL OF HOSPITAL PHARMACY 2000 CANADA, vol. 53, no. 5, 2000, pages 346-348, XP008049461 ISSN: 0008-4123 page 346, left-hand column, paragraph 3 - page 347, left-hand column, paragraph 1 ----- | 1,2,4,5, 8-12,14, 15,18,19 |
| X | YLITALO R: "Bisphosphonates and atherosclerosis" GENERAL PHARMACOLOGY: VASCULAR SYSTEM 2000 UNITED STATES, vol. 35, no. 6, 2000, pages 287-296, XP002268656 ISSN: 0306-3623 page 288, right-hand column, paragraph 5 - page 290, left-hand column, paragraph 1 ----- | 1,2,5, 11-15,19 |
| X | US 2001/034364 A1 (GASPER SHIRLEY R ET AL) 25 October 2001 (2001-10-25) example 8 ----- | 1,2,4, 9-19 |
| A | GALLACHER ET AL: "Side-effects of pamidronate" LANCET, 1989, page 42, XP008049438 cited in the application the whole document ----- | 1-10,14, 19 |
| A | ADAMI ET AL: "The acute-phase response after bisphosphonate administration" CALCIFIED TISSUE INTERNATIONAL, vol. 41, 1987, pages 326-331, XP008049432 cited in the application page 330, left-hand column ----- | 1-10,14, 19 |
| P,X | WO 2004/024165 A (NOVARTIS AG; NOVARTIS PHARMA GMBH; BAULCH-BROWN, CINDY, MAREE; SPENCER) 25 March 2004 (2004-03-25) page 2, paragraph 1; examples 1-5,7 page 8, paragraph 6 - page 9, paragraph 2 pages 9-11; claims ----- | 1-6,8-19 |
| T | MARIANI S ET AL: "Effector 'gamma!' 'delta!' T cells and tumor cells as immune targets of zoledronic acid in multiple myeloma" LEUKEMIA 2005 UNITED KINGDOM, vol. 19, no. 4, 2005, pages 664-670, XP008049442 ISSN: 0887-6924 page 668, right-hand column ----- | 14 |

INTERNATIONAL SEARCH REPORT

ational application No.
PCT/GB2004/005019

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 19 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Inte
nal Application No
PCT/GB2004/005019

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